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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,261	12/09/2003	Stephen M. Testa	50229-418	3335

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,261	TESTA ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *10-24,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claim 1-9 and 25 in the reply filed on June 29, 2005 is acknowledged. The traversal is on the ground(s) that the search required for examination of group I would necessarily include subject matter related to examination of group II and that it would not be considered a serious search burden to search both inventions. This is not found persuasive because searching both of the groups of claims would be an undue burden. Although the search of group I may overlap the search of group II, the searches are divergent and not co-extensive. A search of the prior art that discloses a composition will not provide a thorough search of the distinct method steps in a method of using the composition.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-24, 26 and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 29, 2005.

Claim Objections

Claims 1 and 25 are objected to because of the following informalities: these claims refer to "an ωG of the 3' end of the substrate". The use of the indefinite article

"an" renders the claim ambiguous because it implies there may be more than one ωG. Appropriate correction is required.

Claim 25 is objected to because of the following informalities: the word "comprising" is repeated in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are directed to a ribozyme comprising a recognition element complementary to a non-native target RNA sequence within a substrate. The usage of the phrase "non-native target RNA sequence" is inconsistent with specification, which defines non-native target sequence to be a sequence not recognized by native ribozymes. However, since the compounds of claims 1 and 25 comprise a region complementary to this non-native target RNA, the non-native target sequence recited in the claim must actually be the native target sequence of the modified ribozyme. Given this, it is unknown what sequence or structure this phrase is meant to define. For the purposes of examination this phrase has been interpreted to refer to the sequence that is removed in the trans excision splicing reaction.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble of this claim refers to the method of claim 1. Claim 1 is directed to a compound, not a method. For the purposes of examination this claim has been interpreted as defining the ribozyme of claim 1.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim refers to the ribozyme of claim 1 by a designation that appears to be an abbreviation. It is unknown what this claim is referring to as one of skill in the art would not recognize what ribozyme sequence relates to this abbreviation. If this claim is meant to refer to one particular ribozyme, it is recommended this be done by reference to a SEQ ID NO.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim refers to the ribozyme of claim 1 wherein at least one exon has been removed from the ribozyme. The Group I ribozyme has exons only in its wild-type, self-splicing form. The ribozyme of the instant claims has been modified to perform a *trans* excision reaction. Consequently, the modified ribozyme has no exons to be removed. If this limitation is meant to refer to sequences in addition to the recognition elements recited in claim 1, the claim should be amended to clarify this.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is not a complete sentence. Because the claim is incomplete it is unknown what the claim encompasses and thus it cannot be examined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Sargueil et al. (Journal of Molecular Biology 1993, vol. 233, pages 629-643).

1. Claim 1 is directed to a modified Group I ribozyme capable of catalyzing a specific excision of a non-native target RNA that comprises at least two recognition elements wherein at least one recognition element is complementary to non-native target RNA (interpreted as described above to be the sequence removed by excision) and at least one recognition element stabilizes binding of the ribozyme to a TES reaction intermediate. Claim 25 is directed to an expression cassette capable of expressing such a ribozyme.

2. Sargueil et al. disclose a modified Group I intron that is able to catalyze a complete splicing reaction in *trans*. The substrate is shown in figure 2 and the reaction substrate and product are shown in cartoon form in figure 3. The Group I intron of Sargueil et al. excises the sequence between the arrows in figure 2 and this is considered to be the non-native target RNA. Sargueil et al. also disclose that the modified Group I intron can recognize other substrates besides that normally recognized by the Group I intron. Sargueil et al. disclose at page 635, column 1 that the shortened intron L-30β contains two points of contact with the substrate, the P9.0 interaction known in wild-type Group I introns and the 3' guanosine that interacts with the guanosine binding site used in splicing. These constitute recognition elements that

meet the requirements of claim 1. The L-30β intron is formed by transcription of an expression construct (see page 630, section 2b).

3. Thus, Sargueil et al. disclose and anticipate claims 1 and 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sargueil et al. as applied to claims 1 and 25 above, and further in view of Harley et al. (Am. J. Hum. Genet. 1993, cited on IDS) and Sullenger et al. (Nature 1994, cited on IDS).

4. Claims 1 and 25 are described in the previous 102 rejection. Claims 2-4 limit claim 1 by stating the non-native sequence comprises a single nucleotide, a frameshift mutation or a premature stop codon, which is a particular type of frameshift mutation. Claim 5 limits claim 1 by stating the non-native sequence is the triplet expansion associated with muscular dystrophy.

5. The teachings of Sargueil et al. are described in the previous 102 rejection. Sargueil et al. do not teach that their ribozyme can be used to excise genetic mutations such as those associated with muscular dystrophy.

6. Harley et al. teach that myotonic muscular dystrophy is caused by a CTG triplet repeat in the 3' UTR of a putative protein kinase. Harley et al. further teach that the size of the repeated region is directly correlated with severity and age of onset of the disease.

7. Sullenger et al. teach the use of a Group I ribozyme that has been modified to perform the second step of splicing in *trans*. This modified ribozyme was used to repair a defective *lacZ* mRNA by replacing a truncated 3' exon sequence with a wild-type sequence through a Group I *trans*-splicing reaction. Sullenger et al. teach at page 622, first column that targeted *trans*-splicing can potentially be adapted to correct a broad array of mutant transcripts and suggest that because group I introns recognize splice sites through complementarity to the 5' exon binding site, a *trans*-splicing group I intron can be designed to cleave any transcript at a uridine upstream of a mutation. At the second column of this page Sullenger et al. suggest that such an approach may be useful in correcting genetic deficiencies.

8. It would have been obvious to one of ordinary skill in the art at the time of invention to modify the group I ribozyme of Sargueil et al. that performs a *trans* excision reaction in order to recognize and splice a sequence that will repair genetic mutations, including those associated with muscular dystrophy. Sullenger et al. provide a motivation to use a modified group I intron, teaching that this ribozyme can be modified to splice in *trans* and can potentially be used to gene therapy applications. Harley et al. provides a motivation to treat genetic mutations, teaching that myotonic muscular dystrophy is associated with a triplet repeat and that this disease is correlated with severity and age of onset of the disease. One of skill in the art would be motivated to repair genetic mutations such as single nucleotide mutations and frameshift mutations because each of these types of mutations is well known in the art of genetics to cause disease and it would be desirable to repair these mutations to alleviate the diseases caused by such mutations. One of ordinary skill in the art would have had a reasonable expectation of success in modifying the group I ribozyme to splice in *trans* and recognize substrates other than the natural sequence because both Sargueil et al. and Sullenger et al. have modified the group I ribozyme and demonstrate that these modified ribozymes will function as intended.

9. Thus, the invention of claims 1-5 and 25 would have been obvious, as a whole, at the time of invention.

Claims 1-5, 7 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sargueil et al., Harley et al. and Sullenger et al. as described in the previous 103 rejection and further in view of Testa et al. (Biochemistry 1997, cited on IDS).

10. Claims 1-5 and 25 are described in the previous 103 rejection. Claim 7 limits claim 1 by stating the ribozyme is a modified *P. carinii* ribozyme.

11. The teachings of Sargueil et al., Harley et al. and Sullenger et al. are described in the previous 103 rejection. Testa et al. teach the isolation from *P. carinii* ribosomal RNA a group I intron structure that is capable of performing a self-splicing reaction like the well-characterized group I intron of *Tetrahymena*.

12. The teachings of Sargueil et al., Harley et al. and Sullenger et al. are obvious for the reasons described in the previous 103 rejection. Given the teaching of Testa et al. of the isolation of a group I ribozyme from *P. carinii*, it would have been obvious to one of ordinary skill in the art at the time of invention use any ribozyme from the group I intron family including a modified *P. carinii* ribozyme. One of ordinary skill in the art would have recognized that ribozymes from the same family are functionally equivalent and the use of a group I ribozyme from one source over another is mere design choice. One of ordinary skill in the art would have a reasonable expectation of success in using a *P. carinii* ribozyme because Testa et al. teach that the ribozyme isolated from *P. carinii* is in the group I intron family.

13. Thus, the invention of claims 1-5, 7 and 25 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
September 9, 2005

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PATENT EXAMINER